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This application claims the benefit of U.S. Provisional Application No. 60/507,677 filed September 30, 2003, the text of which application is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to the fields of oncology and molecular biology. More particularly the invention relates to RB2/p130 modulated molecular signatures in lung cancer cells and the diagnosis and prognosis of lung cancer using RB2/p130 modulated molecular signatures. The present invention also relates to strategies for the use of RB2/p130 to regulate the expression of gene products in lung cancer cells.

BACKGROUND OF THE INVENTION

Citation or identification of any scientific reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention.

Lung cancer is one of the leading causes of cancer death in the world. The high mortality rate for lung cancer probably results, at least in part, from the lack of standard clinical procedures for the diagnosis of the disease at early and more treatable stages compared to breast, prostate, and colon cancers (Wiest et al., 1997). There is also extremely poor prognosis associated with diagnosis of the disease, especially in advanced disease. The majority of bronchogenic carcinomas can be classified into four histological types: small cell lung carcinomas, adenocarcinomas, squamous cell lung carcinomas, and large cell carcinomas. Small cell lung carcinomas are a separate entity, whereas the behavior of the other three histological subtypes is similar, for this reason these are grouped within the non-small cell lung cancer (NSCLC) type. The NSCLC accounts for nearly 80% of lung malignant tumors and it is associated with a poor prognosis.

Early detection is difficult since clinical symptoms are often not seen until the disease has reached an advanced stage. Currently, diagnosis is aided by the use of chest x-rays, analysis of the type of cells contained in sputum and examination of the

bronchial passages. Treatment regimens are determined by the type and stage of the cancer, and include surgery, radiation therapy and/or chemotherapy. Because of their lack of molecular specificity, these treatment regimens are not completely effective. For example, a major problem in the chemotherapy of cancers is the delivery of therapeutic agents, such as drugs, in sufficient concentrations to eradicate tumor cells while at the same time minimizing damage to normal cells. Thus, studies in many laboratories are directed toward the design of more specific systems such as antibodies, cytokines, and viruses for targeted delivery of genes into tumor cells. Because of their biospecificity, such systems could in theory deliver therapeutic agents to tumors.

Indeed, it is known in the art that lung cancer is the result of molecular changes in the cell, resulting in the deregulation of pathways which control normal cellular growth, differentiation, and apoptosis. Various genes such as proto-oncogenes and tumor suppressor genes are found to be mutated or have abnormal expression patterns in this disease. Also, the gene therapeutic potential of a number of genes in lung cancer has also been reported (see, for example, US Patents 6,663,856 and 6,797,702). If molecular markers that mediate potential therapeutic effects of genes used in gene therapy programs are available, it can facilitate the selection of the appropriate gene therapy to lung cancer thereby maximizing therapeutic efficacy and minimizing toxicity. Accordingly, there is a need in the art for identification of genes that are regulated by each of the known therapeutic genes for lung cancer so that the expression products can be used as molecular signatures for selecting an appropriate therapeutic gene for modulating the genes expressed in lung cancer cells. The present invention fulfills these needs and further provides other related advantages.

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SUMMARY OF THE INVENTION

In the present invention, a set of molecular signatures modulated by Rb2/p130 in lung cancer cells have been discovered. The identified molecular signatures or markers in a lung tissue sample provide a basis for the use of Rb2/p130 to modulate a gene or genes expressing the molecular signatures.

Accordingly, in a general aspect, the present invention provides a method for

determining whether to use RB2/p130 (either a gene expression system or a protein encoded by the pRb2/p130 to modulate a gene or gene expression pattern in lung cancer cells of a mammalian test subject. The method involves providing molecular signatures modulated by RB2/p130 for lung cancer cells. The molecular signatures include expression products of one or more of the following genes: PCNA, MKK3, B-MYB, CCNF, BUB1B, PLK, NIK, KNSL2, PCSK7, CCNB2, GPRK6, HCFC1. PFAS, DNMT1, KPNA2, STK15, TIEG, BUB1 ELK1, UMPK, PMI, CAMKK2, GSK3B, HADHSC, POLD1, NOL1, EMK1, GRP-R, XRCC3, CHK, MAGEA3/6, PPM1G, TRAF5, ABCF2, TEAD4, PIM1, CCND1, CDR2, PSMB2 and RAF1. The method further involves determining gene or genes expressed in the lung cancer cells of the human test subject and using the RB2/p130 to modulate the gene or the gene expression pattern in the lung cancer cells of the mammalian test subject if it is found that the gene or genes expressed in the lung cancer cells of the mammalian test subject are the same as the one or more of the above listed genes. For example, the genes can be a set of genes such as B-MYB, PCSK7, STK15, ELK1, NOL1, MAGEA3/6, PIM1, CCND1, CDR2, and RAF1, all of which are associated with diseases. The mammal can be pre-treatment or post-treatment for a non-small cell lung cancer, the treatment being surgical operation, chemotherapy, radiation therapy and RB2/p130 gene therapy or combinations these treatments.

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BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Adenovirus-mediated overexpression of RB2/p130. Northern blot and Western blot analyses (a & b) of RB2/p130 in H23, H23-Ad-CMV and H23 Ad-CMV-RB2/p130 non small lung cancer cell line.

Figure 2. Effects of pRb2/p130 enhanced expression in H23 cells. FACS analysis of H23-Ad-CMV (a) and H23-Ad-CMV-Rb2/p130 (b) infected cells. Rb2/p130 over-expression resulted in 81.2% of the cells accumulated in the G0/G1 phase of the cell cycle when compared to the empty adenovirus (54%). The analysis was performed in triplicates with comparable results.

Figure 3. Global comparison of gene expression in H23 vs. H23-Ad-CMV and H23-Ad-CMV vs. H23-Ad-CMV-RB2 cells. Each dot corresponds to the Cv3

fluorescent intensity of one single element on the oligonucleotide microarray. A twofold change in expression is indicated with parallel lines marked as 2.

Figure 4. Validation of oligonucleotide microarray results of 11 selected genes by semi quantitative RT-PCR. RT-PCRs were performed using DNAse treated total RNA of H23, H23-Ad-CMV and H23-Ad-CMV-Rb2/p130 non small lung cancer cell line. Amplified fragments of B-MYB (194 bp), Cyc B2 (217 bp), Cyc D1 (463 bp), GRPR (377 bp), KPNA2 (304 bp), MKK3 (219 bp), NIK (317 bp), PCNA (420 bp), PIM1 (324 bp), PLK (154 bp) and RAF1 (280 bp) genes are indicated. ACT-β (626 bp) and HPRT (349 bp) genes were used as internal controls and were amplified from the same samples..

Figure 5. Validation of oligonucleotide microarray data by western blot analysis. One hundred μg of protein extracts from H23, H23-Ad-CMV and H23-Ad-CMV-Rb2/p130 cells were loaded onto SDS-PAGE gels and immunoblotted with antibodies anti B-MYB, E2F-1, MAGEA 3/6, MKK3, NIK, PCNA, PLK and RAF1. Anti HSP-70 was used as internal control. The analysis was performed in duplicates with comparable results.

DETAILED DESCRIPTION OF THE INVENTION

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The present invention is based on the discovery of some of the molecular signatures or markers modulated by Rb2/p130 in non-small cell lung cancer (NSCLC) cells and the use of the molecular signatures as a basis for the administration of Rb2/p130 to modulate genes or gene expression patterns in the in non-small cell lung cancer cells.

Changes in cell phenotype in cancer are often the result of one or more changes in the gene expression of the cell. Some genes are expressed in tumor cells, and not in normal cells. In addition, different genes directly or indirectly induce cancer growth while others directly or indirectly suppress cancer growth. In fact, immunohistochemical analysis of the expression patterns of the Rb family members (pRb/p105, p107, and pRb2/p130) in 235 specimens of lung cancer (Baldi et al., 1996) and the expression pattern of pRb2/p130 in 158 specimens of human lung cancer showed an inverse correlation between the histological grading of the tumors, the

development of metastasis, and the level of expression of pRb2/p130 (Baldi et al., 1997). A statistically significant inverse relationship between the histological grading and the expression of pRb/p105, p107 and pRb2/p130 was found in fine needle aspiration biopsies of squamous cell carcinoma patients (Minimo et al., 1999).

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The invention described herein relates to the identification of a set of genes expressed in NSCLC cells that are modulated by Rb2/p130.In an aspect, the present invention simplifies prognosis determination by providing an identified set of genes whose expression in lung cancer cells can be modulated (down regulated or upregulated) which may predict clinical outcome as defined by, cell proliferation, tumor metastasis, recurrence, or death.

The protein and amino acid sequences of RB2/p130 and expression constructs of pRb2/p130 are known in the art (see, for example U.S. Patent 5,532,340). For example, to obtain expression constructs, a full length cDNA sequence of Rb2/p130 is subcloned into suitable retroviral or adenoviral vectors (MSCVneoEB ad MSCVPac) and such expression vectors are known to one skilled in the art.

In the present invention, RNA expression phenotyping was performed using high density oligonucleotide microarrays generated from quantitative expression data on over 3200 genes, which have been analyzed to identify specific genes down-regulated by RB2/p130 expression. The expression gene set can have several uses including, but not limited to, the following examples. The expression gene set may be used as a prognostic tool for lung cancer patients, to make possible more finely tuned diagnosis of lung cancer and allow physicians to tailor treatment to individual patients' needs. The invention can also assess the efficacy of NSCLC treatment by determining progression or regression of the lung cancer in patients before, during, and after the NSCLC cancer treatment. Another use of the expression gene set can be in the biotechnology and pharmaceutical industries' research on disease pathway discovery for therapeutic targeting. The invention can identify alterations in gene expression in lung cancer and can also be used to uncover and test candidate pharmaceutical agents to treat the lung cancer.

As used herein, a subject is a human although non-human mammals such as

primate, rabbit, dog, cat, cow, horse, pig, sheep, goat and rodents are also contemplated. Preferably the subject is a human either suspected of having lung cancer or having been diagnosed with lung cancer. Methods for identifying subjects suspected of having lung cancer may include physical examination, subject's family medical history, subject's medical history, lung cancer biopsy, or a number of imaging technologies such as tomography ultrasound, magnetic resonance imaging, magnetic resonance spectroscopy, etc. Conventional diagnostic methods for lung cancer and the clinical delineation of lung cancer diagnoses are well known to those of skill in the medical arts.

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As used herein, endometrial tissue sample is tissue obtained from an endometrial tissue biopsy using methods well known to those of ordinary skill in the related medical arts. In some instances a sample from the biopsy may be sufficient for assessment of RNA expression without amplification, but in other instances the lack of suitable cells in a small biopsy region may require use of RNA conversion and/or amplification methods or other methods to enhance resolution of the nucleic acid molecules. Such methods are well known to those of ordinary skill in the art and include, but are not limited to: direct RNA amplification, reverse transcription of RNA to cDNA (RT PCR), amplification of cDNA, or the generation of radio-labeled nucleic acids.

In the context of the present invention, "determining expression of gene or genes (or a set of nucleic acid molecules) in the lung cancer cells" means identifying RNA transcripts in the tissue sample by analysis of nucleic acid or protein expression in the tissue sample. As used herein, "set" refers to a group of genes classified in under a given category as listed in Table 2 herein. In some embodiments a set can include one or more categories or a combination of these categories.

The expression of the set of nucleic acid molecules in the sample from the lung cancer subject can be compared to the expression of the set of nucleic acid molecules in a sample of lung tissue that is non-cancerous. As used herein, non-cancerous lung tissue means tissue determined by one of ordinary skill in the medical art to have no evidence of lung cancer based on standard diagnostic methods including, but not limited to, histologic staining and microscopic analysis.

In the present invention, standard hybridization techniques of microarray technology are utilized to assess patterns of nucleic acid expression and identify nucleic acid marker expression. Microarray technology, which is also known by other names such as DNA chip technology and gene chip technology is well known to those of ordinary skill in the art and is based on, but not limited to, obtaining an array of identified nucleic acid probes on a fixed substrate, labeling target molecules with reporter molecules (e.g., radioactive, chemiluminescent, or fluorescent tags such as fluorescein, Cye3-dUTP, or Cye5-dUTP), hybridizing target nucleic acids to the probes, and evaluating target-probe hybridization. A probe with a nucleic acid sequence that perfectly matches the target sequence will, in general, result in detection of a stronger reporter-molecule signal than will probes with less perfect matches. Microarray technology is well known to one skilled in the art. The present invention also contemplates protein microarrays for analyzing molecular signatures in lung cancer cells or tissue.

In some instances, the microarray data can be validated using semi quantitative RT-PCR analysis, Northern blot analysis and/or Western blot analysis. These validation procedures are preferably used in instances where the determination of the gene expression level of specific pRb2/p130 target genes are desired.

WORKING EXAMPLES

The following non-limiting examples and data are provided to illustrate various aspects and features relating to the methods of the present invention and as a further guide to one of ordinary skill in the art, and are not to be construed as limiting the invention in any way.

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Example 1: Effects of RB2/p130 adenoviral transduction on the H23 lung adenocarcinoma cell line

The human lung adenocarcinoma cell line H23 has been described previously (Claudio et al., 2000). The packaging cell line 293 (primary embryonal human kidney cells) transformed by sheared human adenovirus type 5 has been also previously described (Claudio et al., 1999). H23 cells were maintained in DMEM supplemented with 10% fetal bovine serum, 2 mM L-glutamine. 293 cells were maintained in

DMEM supplemented with 10% heat inactivated fetal bovine serum, 2 mM L-glutamine.

Adenoviruses were generated by subcloning the full-length ORF of the *RB2/p130* gene into the pAd.CMV-Link1 vector to form the Ad.CMV-*RB2/p130* virus, as described previously (Claudio et al., 1999, Davis et al., 1998). The pAd.CMV-Link1 vector alone (to produce the Ad-CMV virus) was used as a negative control to assay the effects of viral infection alone without delivering a transgene. Adenoviruses were expanded, purified and tittered as previously described (Claudio et al., 1999).

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Flow cytometry analysis (FACS) of exponentially growing H23 cells or H23 cells transduced with Ad-CMV or Ad-CMV-Rb2/p130 were carried out as previously described (Claudio et al., 1996). Briefly, 5X10⁵ cells were seeded and 24 hours after the cells were transduced with 50 MOI (multiplicity of infection) of adenoviruses. 48 hours after transduction, cells were collected and analyzed using a Coulter Flow cytometer.

For Northern blot analysis, H23 cells were grown to 60% confluency then infected with 50 MOI of adenoviruses carrying the *RB2/p130* gene or with the control Ad-CMV. After 14 h, medium was changed, and cells were harvested at 48 hours from the transduction. DNAse-treated total RNA from H23, H23-Ad-CMV and H23-Ad-CMV-Rb2/p130 transduced cells were extracted using TRIzol (Life Technologies, Inc, Grand Island, NY) according to manufacturer's protocol. Northern blot analysis was performed as previously described (Claudio et al., 1994).

Western blot analysis of exponentially growing H23 cells or of H23 cells transduced with Ad-CMV or Ad-CMV-Rb2/p130 were carried as previously described (Claudio et al., 1999). Extracts were normalized for protein content by Bradford analysis (Bio-Rad Laboratories, Inc., Melville, New York) and commasie blue gel staining. Primary anti-B-MYB, E2F-1, KPNA2, MKK3, NIK, PCNA, PLK, RAF1 (Santa Cruz Biotechnology, Inc., Santa Cruz, CA), anti-MAGE-A (Upstate, Lake Placid, NY) and anti-HSP70 (Oncogene Science, Cambridge, MA) were used following manufacturer's instructions.

H23 cells were plated at a density of $5x10^5$ in four 10-cm tissue culture dishes.

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Cell were transduced with 50 MOI of the control Ad-CMV or Ad-CMV-RB2/p130 and harvested after 48 h. Two tissue culture dishes were used to extract mRNA. One tissue culture dish was used to extract the proteins and one for FACS analysis.

Northern blot analysis of samples transduced with *RB2/p130* showed an increased expression of the *RB2/p130* transcript more than 20 fold with respect to the control (Fig. 1a). Western blot analysis showed more than 100 fold enhanced expression of pRb2/p130 in the Ad-CMV-*RB2/p130* transduced cells (Fig. 1b). To confirm the effects of pRb2/p130 enhanced expression in H23 cells we performed FACS analysis. Figure 2 shows that adenoviral Rb2/p130 transduction resulted in 81.2% of the cells accumulated in the G0/G1 phase of the cell cycle when compared to the control (54%).

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Example 2: Oligonucleotide microarray assay following enhanced expression of pRb2/p130 in a human lung adenocarcinoma cell line

Before submission of RNA samples for analysis protein extracts prepared from replicate plates of the corresponding cell culture were analyzed for expected enhanced expression of pRb2/p130 using western blots. Oligonucleotide-based microarrays were purchased from Mergen (Mergen Ltd. San Leandro, CA). ExpressChip H05000 DNA microarray system was used for this study. This array contains more than 3200 genes that are involved in a variety of different processes. DNase-treated total RNA (20µg) from H23 (parental cells), H23 cells transduced with Ad-CMV or Ad-CMV-RB2/p130 cell lines 48 hours after transduction were extracted using TRIzol (Life Technologies, Inc, Grand Island, NY) according to manufacturer's protocol. RNA integrity was verified for lack of degradation by formaldehyde gel electrophoresis. The biotin-labeled cRNA probes preparation, hybridization and array scanning were performed using Mergen Labeling/Hybridization/Detection Service.

Data acquisition and data analysis were performed using Imagene software (Biodiscovery Inc., Marina del Rey, CA) and Mergen's *Express*Data[™] software (Mergen Ltd. San Leandro, CA). Briefly, data were processed for local background correction and normalization. Raw-Spot for each gene was calculated as the mean signal of the spot values minus that of local background. The I_{max} value was set to

65,000, after local background removal. A Normalization Coefficient (N) was applied to either the control population or to sample spot raw values to compensate for slide-to-slide and probe-to-probe variations. The Normalization coefficient was applied only if (Raw_spot/N) < I_{max}, otherwise values were set to I_{max}. Normalized values ≤0 were excluded from the analysis. Genes regulated by adenovirus transduction (Ad-CMV) with respect to the parental cell line were removed from the analysis. Spots with Mean Intensities > 45,000 were excluded for the ratio analysis. The expression ratios calculated with corrected values < mean of the local background on both channels were not used. Expression ratio of the analyzed genes were calculated comparing genes' expression values of H23 cells transduced with RB2/p130 with those of parental H23 or H23 cells transduced with Ad-CMV. A 2 fold or higher levels of target genes' expression ratio was considered significant, in accordance with most of the literature.

H23 cells were transduced with Ad-CMV or Ad-CMV-*RB2/p130*. Forty-eight hours later, 20 μg of DNA-free total RNA from H23, H23-Ad-CMV or H23-Ad-CMV-*RB2/p130* cells was reverse-transcribed and the double-strand cDNA was used as template to generate Cy3-labeled cRNA probes and then hybridized to the Mergen H05000 oligonucleotide-based microarray containing more than 3200 genes that are involved in a variety of different processes. Analysis was performed by Mergen Ltd, San Leandro, CA. Microarray experiments were performed comparing H23 vs. H23-Ad-CMV; H23-Ad-CMV vs. H23-Ad-CMV-*RB2/p130*; and H23 vs. H23-Ad-CMV-*RB2/p130* cells. Duplicate experiments were carried out on a single total RNA preparation from the cells.

In this study 40 genes were downregulated more than 2.0-fold (Table 1). Figure 3 shows the plots of the differential expression of 3263 genes in H23-Ad-CMV vs. H23-Ad-CMV-RB2/p130 cells and H23 vs. H23-Ad-CMV-RB2/p130 cells. Overall, the expression of the majority of the spotted genes was not altered by RB2/p130. Modulated genes were classified in table 2 on the basis of a well documented and established biological or pathological function of the encoded protein. The genes downregulated by pRb2/p130 enhanced expression belong mainly to the following categories: cell division, signaling and communication, cell structure and motility,

gene expression, metabolism, and disease.

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Example 3: Validation of the oligonucleotide microarray assay using semi quantitative RT-PCR and western blot analysis..

RT-PCR was used to analyze target gene expression in the present study. A 2 μ g aliquot of DNAse-treated total RNA from each sample was reverse-transcribed for single stranded cDNAs using M-MLV reverse transcriptase (Invitrogen, Carlsbad, CA) according to manufacturer's protocol. The same cDNA product obtained from each sample was used for subsequent PCR amplification with the primer sets prepared for the target gene and β -actin (Act- β)/HPRT housekeeping genes. The amplification of the β -actin and HPRT genes were used as double internal control. Ratio between the samples and each housekeeping gene was calculated to normalize for initial variations in sample concentration and as control for reaction efficiency. Primer sequences were designed using the software Primer 3 (developed by Steve Rozen, Helen J. Skaletsky) available on-line at http://www-genome.wi.mit.edu. Primer sequences can be provided upon request. PCR reaction conditions were individually optimized for each gene product studied and the number of PCR cycles was setup to be within the linear range of product amplification.

In each experiment, possible DNA contamination was determined by a control
reaction in which reverse transcriptase was omitted from the reaction mixture. PCR
products were loaded onto ethidium bromide stained 1.5% agarose gels.

Densitometric analysis of the PCR products were performed using an Alpha Imager
system (Alpha Innotech Corporation, San Leandro, CA) and the ImageJ v1.29
software (developed by Wayne Rasband) available on-line at

http://rsb.info.nih.gov/ij/. All PCR products were purified using QIAquick PCR
purification kit (Qiagen, Santa Clarita, CA) and their identities verified by automated
DNA forward and reverse sequencing using a dideoxy terminator reaction chemistry
for sequence analysis on the Applied biosystem Model 373A DNA sequencer.

E. coli dH5alpha cells transformed with recLic B-GFP constructs were cultured or fermented by overnight culturing process in LB media. The fermentation was continued for 12 h and harvested at a cell density of 10⁴. Two liters of cell culture

or fermentation broth were divided into 1 liter containers//bottles and centrifuged at 10,000 rpm for 30 min in a centrifuge. The supernatant was discarded and the pellet was used to recover the carrier protein.

To determine the gene expression level of specific pRb2/p130 target genes, semiquantitative RT-PCR analysis was used. A panel of 11 genes, randomly selected 5 among the 40 identified by microarray analysis, was analysed. We confirmed this by RT-PCR downregulation of BMYB, Cyc B2, Cyc D1, GRPR, KPNA2, MKK3, NIK, PCNA, PIM, PLK, and RAF-1 (Figure 4). Genes highly downregulated (range between 6-and 17-fold) in microarray analysis such as PCNA, MKK3, B-MYB, and NIK showed a comparative downregulation in semiquantitative RT-PCR analysis 10 between 7-and 3.5-fold. Genes still downregulated in microarray analysis, but at a lower extent such as RAF-1, PIM1, CycD1, GRPR, KPNA2, and CycB2, showed a comparable downregulation in semiquantitative RT-PCR analysis between 3.4-and 2.0-fold. PLK, which showed a high downregulation ratio in microarray analysis, failed to be validated by semiquantitative RT-PCR. In fact, PLK showed almost a 15 two-fold difference expression level by RT-PCR. Of the 11 transcriptionally downregulated genes that were studied by RT-PCR analysis, only seven genes (B-MYB; KPNA2, MKK3, NIK, PLK, and RAF-1) were found expressed by Western blot analysis at a lower level upon enhanced pRb2/p130 expression with a ratio between 1.9-and 3.0-fold (Figure 5). As the MAGE gene family is composed of 23 20 related genes divided into four clusters and the MAGE-A subfamily comprises 12 genes highly identical in their coding sequence, we were not able to perform RT-PCR on this gene family, but we could confirm by Western blot analysis the contingent downregulation of MAGEA-3/6 to enhanced pRb2/p130 expression. Surprisingly, PCNA that was highly down-regulated in the microarray analysis, also appearing 25 modulated in RT-PCR, showed no protein expression changes upon enhanced pRb2/p130 expression. However, it has been shown that PCNA has a relatively long half-life that can extend beyond the S phase into the M phase and beyond into the G0 phase of cells in rapidly proliferating tumors.

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All publications, patents and patent applications mentioned in the specification

are indicative of the level of those skilled in the art to which this invention pertains. All publications, patents and patent applications referred to herein are incorporated herein by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference. While this invention has been described with a reference to specific embodiments, it will be obvious to those of ordinary skill in the art that variations in these methods and compositions may be used and that it is intended that the invention may be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications encompassed within the spirit and scope of the invention as defined by the claims.

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Table 1. Downregulated genes by RB2/p130 adenovirus-enhanced expression

I M15796 Proliferating cell nuclear antigen FCNA 16.4 17.5 2 L36719 Vinybe wixan myeloblastosis viral oncogene homologil, β MixKx3 12.4 192 2 X13239 Vinybe wixan myeloblastosis viral oncogene homologil, β BUBB 8.9 6.6 8.7 5 AF053306 Budding uninklished by beatminidazoles I (yeast homologil, β BUBB 8.9 6.7 7.6 6 L10559 Polo (Drosophia)-like kinase NIK 5.6 7.6 8 D1468 Rinesin-like 2 Rinesin-like 2 NIK 5.6 7.6 10 AF002822 Cyclin BZ Cyclin BZ CCCNSS 5.7 7.7 11 L16662 G protochien convertures subilisin/kexin type 7 CCCNSZ 5.7 7.7 12 L20010 Host cell factor CI FCAR antidotranscriense FCAR antidotranscriense 1.7 7.8 7.9		GenBankTM ID	Gene description	Gene symbol	Ratio I	Ratio I Ratio 2	Average
1.156719 Mitogen-activated protein kinase kinase 3 MKK23 12.4 115 X13233 V-moyo axian myelobiasosis viral ouroegene homolog-like 2 BMATB BMATB 12.4 115 X13235 V-moyo axian myelobiasosis viral ouroegene homolog, β BMATB BMATB 2.5 Z10714 Cyclin F BMAGing uninhibitate kinase	1 -	7075 IM	Proliferating cell anglear antigen	PCNA	16.4	17.5	16.9
Xi3393 V-myb a wian myeloblastosis viral oncogene homolog-like 2 B-MYB 8.2 17.5 Acydin 6 Cyclin 7 Cyclin 7 Cyclin 7 Cyclin 8 PLK 6.5 A 195559 Miogen-activated protein kinase kinase kinase kinase 4 NIK S.6 NIK Y 10256 Kinesin-like 2 Kinasin-like kinase NIK S.6 NIK Y 10256 Kinesin-like 2 Kinasin-like kinase NIK S.6 S.6 U 133849 Proproducion convertase subilisin/kexin type 7 CCNB2 CCNB2 S.6 V 120840 Cyclin B CCNB2 S.6 CCNB2 S.3 L 220010 FGAR amidotraneferase FGAR amidotraneferase FGAR Amidotraneferase BPFAS 3.7 L 20010 FGAR amidotraneferase FARIA KRF6 S.7 ARVIA 3.2 ARVIA 3.3 ARVIA 3.2 ARVIA 3.2 ARVIA 3.2	٠,	1 36719	Mitogen-activated protein kinase kinase 3	MKK3	12.4	19.2	15.8
256714 Cyclin F CONF 66 256714 Cyclin F Cyclin F CONF 66 L195359 Budding unimhibited by benzimidazoles I (yeast homolog), β PUBBB 89 L19536 Kingen-like 2 Polo (Drosophial-like kinase NIK 5.6 D14678 Kingen-like 2 Proprotein convertase subtilisin/kexin type 7 CCNB2 5.3 U03384 Proprotein convertase subtilisin/kexin type 7 CCNB2 5.3 L20010 Host cell factor CI Processed Processed Research Processed Research L20010 Host cell factor CI Processed Research Processed Research L20010 Host cell factor CI Processed Research Processed Research L20010 Host cell factor CI Processed Research Processed Research L20010 Host cell factor CI Processed Research Processed Research L20010 Host cell factor CI Processed Research Processed Research L20010 Host cell factor CI Processed Research Processed Research L20010 Host cell factor CI<	۱ ۳	X13293	V-myh avian myeloblastosis viral oncogene homolog-like 2	B-MYB	8.2	13	10.6
AF673306 Búdding uninhibited by benzimidazoles I (yeast homolog), β BUBIB 8.9 A 109559 Polo (Crosophia)-like kinase NIIX 5.6 Y 10256 Miogen-activated protein kinase kinase kinase 4 NIX 5.6 Y 10258 Polo (Crosophia)-like kinase NIX 5.6 U 13689 Perportoien convertues aubitisin/kexin type 7 PCCNB2 5.3 U 12682 C protein-coupled receptor kinase 6 PCNB2 CCNB2 5.3 L 12682 C protein-coupled receptor kinase 6 PCNB2 CCNB2 5.3 L 12682 C protein-coupled receptor kinase 6 PCNB2 CCNB2 3.3 L 12682 DNA (cryotine-c-b-methyltransferase 1 PFAS 3.7 L 12682 DNA (cryotine-c-b-methyltransferase 1 PFAS 3.7 L 12682 DNA (cryotine-c-b-methyltransferase 1 PRNAT 3.7 L 12693 RAF01468 Scring-khreonine kinase 1 PRNAT 3.7 L 12694 Budding uninhibited by beraimidacoles I (veast homolog) PRNAT 3.4 L 12694 Budding uninhibited by ber	4	236714	Cyclin F	CCNF	9.9	8.7	7.6
19359 Polo (D'osophia)-like kinase kinase kinase kinase 4 NIK 515 Kintsian-like 2 19359 Polo (D'osophia)-like kinase kinase kinase kinase 4 NIK 515 Kintsian-like 2 191849 Proprotien convertuae subtilisin/kexin type 7 CCNB2 213849 Coprotien convertuae subtilisin/kexin type 7 CCNB2 213849 Coprotien convertuae subtilisin/kexin type 7 CCNB2 213840 CCNB2 CCNB2 213840 CCNB2 CCNB2 213840 CCNB2 CCNB2 213840 CORS 2 CONB2 CCNB2	· v	AF053306	uninhibited by benzimidazoles 1 (yeast homolog),	BUBIB	8.9	9	7.4
Vinoside	ى د	1.19559	;	PLK	6.5	7.5	7
Did678 Kinesin-like 2 KINSL2 5 019678 Kinesin-like 2 AF002620 CCNB2 5.3 04700262 Cyclin B2 Cyclin B2 CCNB2 5.3 1 L16862 G protein-coupled receptor kinase 6 HCFCI 3.5 1 L20010 Host cell factor CI HCFCI 3.2 2 L20010 Host cell factor CI PFAS 3.3 3 L20010 HOST cell factor CI PFAS 3.3 4 K63692 DNA (cytosine-5-)-methyltransferase I PFAS 3.2 5 U05359 Scring-threonine kinase I5 Scring-threonine kinase I5 STK15 3.7 5 U05359 Scring-threonine kinase Is STK15 3.7 STK15 3.3 6 M25269 Ladding uninhibited by benazimidacoles I (yeast homolog) BUMPK 3.2 7 U21847 TGFB-inducible early growth response ILBL STK15 3.2 8 M25269 Ladding uninhibited by benazimidacoles I (yeast homolog) BUMPK 3.2 9 L0326 Ladding uninhibited by benazimidacoles I (yeast homolog) CAMKK2	, ,	V10256	nase kinase kinase kinase	NIK	5.6	9.6	9.9
U33849 Proprotein convertuse subtilisin/kexin type 7 PCSK7 44 V33849 CrOpin 82 Cyclin 82 S.3 A F002822 Cyclin R2 Cyclin 82 S.3 2 L20010 Host cell factor CI PFAS 3.3 2 L20013 FOAR amidotusicrasse PFAS 3.3 3 AB002359 FOAR Amidotusic kinase I PFAS 3.3 5 U20014 FOAR Samidotusic kinase I PFAS 3.3 5 U200259 Karyopherin α 2 PRAS 3.3 5 U20144 Scrinchtreonic kinase I (yeast homolog) PNAT 3.5 6 AF01148 Sariothreonic kinase I (yeast homolog) BUBI 4.3 7 U2014 Sariothreonic kinase I (yeast homolog) BUBI 4.3 8 P66078 Budding uninhibited by bernainidacoles I (yeast homolog) BLKI 1.0 9 M22569 ELKI, member of ETS oncogene family UMRK 2.1 1 X1804 Calcium/calmochilin-dependent protein CAlcium/calmochilin-dependent protein CAlcium/calmochilin-dependent protein CAlcium/calmochilin-dependent protein CAlcium/calmochil	· 00	D14678	Kinesin-like 2	KNSL2	Ś	6.7	5.8
A F002820 Cyclin B2 Cyclin B2 Cyclin B2 L16862 G protein-coupled receptor kinase 6 HCFCI L20010 Host cell factor C1 Host cell factor C1 FCAR amidotransferase HCFCI L20010 Host cell factor C1 FCAR amidotransferase 1 HCFCI S M802359 FCAR amidotransferase 1 S LOSS Karyopherin a 2 S LOSS Karyopherin a 2 S CAF011468 Serine(threonine kinase 15 AF011468 Serine(threonine kinase 15 AF011468 Serine(threonine kinase 15 AF011468 FCAF011468 FOLOST TCFE-Inducible arily growth response B M2269 Unding uninhibited by benzinindacoles 1 (yeast homolog) B FOLOST ELKI B M2269 Unding monologophate kinase D VAGORDA Putative receptor protein A S018330 Calcium/calmodulin-dependent protein kinase kinase 2, β A B018330 Calcium/calmodulin-dependent protein kinase kinase 2, β A B018330 Calcium/calmodulin-dependent protein kinase kinase kinase 2, β	0	1133849	Proprotein convertuse subtilisin/kexin type 7	PCSK7	4.4	6.5	5.4
Li6862 G protein-coupled receptor kinase 6 GPRK6 3.5 Li20010 Host cell factor CI 3.2 HCFC1 3.2 AB002359 FGAR amidotransferase KRPNA2 3.5 X63692 DNA (cytosine-5-)-methyltransferase 1 KRPNA2 3.5 AF011468 Karyopherin a Z Srinck/hreonine kinase 15 3.7 V109559 Karyopherin a Z Srinck/hreonine kinase 15 3.7 V21847 TGFB-induckible early growth response 171EG 3.3 V21847 TGFB-induckible early growth response 1 (2000) 1 (2000) 1 (2000) 3.3 M22669 Budding uninhibited by benzimidazoles 1 (yeast homolog) BUBI 4.3 M2269 ELKI, member of ETS oncogene family UMPK 3.2 X51804 Putative receptor protein Calcium/calmodulin-dependent protein kinase kinase 2, β CAMKK2 2.1 AF001903 L-3-hydroxyacyl-Coenzyme A dehydrogenase, short chain POLDI 2.7 AF001903 L-3-hydroxyacyl-Coenzyme A dehydrogenase, short chain POLDI 2.7 AF01904	, ⊆	A F007822	Cyclin B2	CCNB2	5.3	4.2	4.7
L20010 HOSt cell factor CI AB002359 FOAR amidotransferase AB002359 K63592 FOAR amidotransferase AB002359 K63592 FOAR amidotransferase Manual AF011468 FOAR amidotransferase FOAR AF01146 AF011469 Karyopherin α 2 Scrine(threonine kinase 15 1005539 Karyopherin α 2 Scrine(threonine kinase 15 101347 TOFE-inducible early growth response I (FRE) 3.7 1021847 TOFE-inducible early growth response I (FRE) BUBH 4.3 1021847 TOFE-inducible early growth response I (FRE) BUBH 4.3 M32269 Uridine monophosphate kinase I (FRE) BUBH 3.2 AS13350 Calcium/calmodulin-dependent protein kinase kinase 2, β CAMKK2 2.1 AF001903 L-3-hydroxecy-(Concaryme A dehydrogenase, short chain POLDH 2.7 AF001903 L-3-hydroxecy-(Concaryme A dehydrogenase, short chain POLDH 2.7 M81735 Polymerase (DNA directed), δ 1, catalytic submif AF035556 A-1-3-hydroxecy-(Concaryme A de	: =	1.16862	G protein-coupled receptor kinase 6	GPRK6	3.5	5.7	4.6
AB002359 FGAR amidotransferase AB002359 FGAR amidotransferase AB002359 FGAR amidotransferase I AKB002359 KGARS AKB002359 AKGPAR 3.7 AKB00259 AKGPAR 3.7 AKD0359 AKGPAR 3.7 AKD0359 AKGPAR 3.7 AKD0359 AKGPAR 3.7 AKD0450 AKCC3 ACC3 ACC	: 2		Host cell factor Cl	HCFCI	3.2	5.9	4.5
X63692 DNA (cytosine-5-)-methyltransferase 1 DNAMTI 3.5 109559 Karyopherin α 2 2 STRM3 3.7 1019559 Karyopherin α 2 Serine/Mreonine arily growth response 121847 3.7 1021847 TGFB-inducible early growth response 1 (yeast homolog) BUBI 4.3 F046078 Budding uninhibited by benzimidazoles 1 (yeast homolog) BUBI 4.3 M22269 ELKI, member of ETS oncogene family UMPK 2.4 X51804 Uridine monophosphate kinase UMPK 2.4 X51804 Putative receptor protein UMPK 2.4 AB018330 Calcium/calmodulin-dependent protein kinase kinase 1 β CAMKK2 2.1 AF018330 Calcium/calmodulin-dependent protein kinase kinase (DNA directed), δ 1, catalytic submit HADHSC 2.2 AF018330 Calcium/calmodulin-dependent geograph finase (complementing defective repair in Chinese hamster cells 3 CHK 2.4 AF03556 Choline kinase Alongonia kinase In Commerly 2C), magnesium-dependent, gamma isoform TRAF5 2.2 A100359 ATE-binding c	2		FGAR amidotransferase	PFAS	3.7	٠	4.3
U09559 Karyopherin α 2 KPNA2 3.5 AF011468 Serine/Intronine kinase 15 STK15 3.7 AF011468 Serine/Intronine kinase 15 TIEG 3.7 F046078 Budding uninhibited by benzimidazoles 1 (yeast homolog) BUB1 4.3 F046078 Budding uninhibited by benzimidazoles 1 (yeast homolog) BUB1 4.3 M25269 ELK1, member of ETS oncogene family UMPK 3.2 D78335 Uridine monophosphate kinase BLK1 UMPK 3.2 X51804 Putative receptor protein CAMKK2 2.1 L33801 Calcium/calmodulin-dependent protein kinase short chain PMI CAMKK2 2.1 L33801 Calcium/calmodulin-dependent protein kinase short chain HADHSC 3.2 M31310 Nucleolar protein 1 L.3-hydroxyacyl-Coenzyme A dehydrogenase, short chain POLD1 2.7 M31310 Nucleolar protein L.3-hydroxyacyl-Coenzyme A dehydrogenase, short chain HADHSC 3.2 M31310 Nucleolar protein A Follon 1.3-hydroxyacyl-Coenzyme A dehydrogenase, short chain 1.3-h	4		DNA (cytosine-5-)-methyltransferase 1	DNMTI	3.5	4.9	4.2
AF011468 Serine/threonine kinase 15 STK15 3.7 U21847 TGFB-inducible early growth response TGFB-inducible early growth response TGFB-inducible early growth response 1.0 F046078 Budding uninhibited by benzimidazoles I (yeast homolog) BudBi 4.3 F046078 Budding uninhibited by benzimidazoles I (yeast homolog) BLKI 3.1 D78335 Uridine monophosphate kinase PM 2.4 AR01804 Putative receptor protein PM 2.4 AR01805 Putative receptor protein CAMKK2 2.1 AR01903 L-3-hydroxyacyl-Coenzyme A dehydrogenase, short chain HADHSC 3.2 AR01903 L-3-hydroxyacyl-Coenzyme A dehydrogenase, short chain HADHSC 3.2 AR1713 Polymerase (DNA directed), δ 1, catalytic subunit POLDI 2.7 M81735 Polymerase (DNA directed), δ 1, catalytic subunit MOLDI 2.7 M32110 Nucleolar protein I XS7630 ELKL motil kinase XRCC3 3.2 M73481 Cx-ray repair complementing defective repair in Chinese hamster cells 3 XRCC3 3.5 </td <td>15</td> <td></td> <td>Karvopherin a 2</td> <td>KPNA2</td> <td>3.5</td> <td>4.1</td> <td>3.8</td>	15		Karvopherin a 2	KPNA2	3.5	4.1	3.8
U21847 TGFB-inducible early growth response TIEG 3.3 F046078 Budding uninhibited by benzimidazoles I (yeast homolog) BUBI 4.3 F046078 Budding uninhibited by benzimidazoles I (yeast homolog) UMPK 3.2 M25269 ELKI, member of ETS oncogene family UMPK 3.2 X51804 Putative receptor protein PMI 2.4 AB018330 Calcium/calmodulin-dependent protein kinase Kinase 3 β CAMKK2 2.1 L23801 Calcium/calmodulin-dependent protein by Coenzyme A dehydrogenase, short chain CAMKK2 2.1 AF001903 L-3-hydroxyacyl-Coenzyme A dehydrogenase, short chain POLDI 2.5 M81735 Polymerase (DNA directed), δ i, catalytic subunit POLDI 2.5 M81735 Nucleolar protein I XSTS 2.5 M73481 Gastrin-releasing peptide receptor Activity Strain S	9	_	Serine/threonine kinase 15	STK15	3.7	4	00.
F046078 Budding uninhibited by benzimidazoles I (yeast homolog) BUBI 4.3 M2269 ELKI, member of ETS oncogene family Under the member of ETS oncogene family 1.2 D78335 Uridine monophosphate kinase PMI 2.4 AB01830 Calcium/calmodulin-dependent protein CAMKK2 2.1 AR301933 Calcium/calmodulin-dependent protein CAMKK2 2.1 AF001903 L-3-hydroxyacyl-Coenzyme A dehydrogenase, short chain HADHSC 3.2 AF001903 L-3-hydroxyacyl-Coenzyme A dehydrogenase, short chain POLDI 2.7 M81735 Nucleolar protein CAMKK2 2.1 M32110 Nucleolar protein ELKL motif kinase CARA M73481 Gastrin-releasing peptide receptor AF03586 X-ray repair complementing defective repair in Chinese hamster cells 3 XRCC3 2.5 M73481 Choline kinase Choline kinase Choline kinase 1.7 1.7 U10339 Melanoma antigen, family A,3/6 Y13936 ATP-binding cassette, sub-family F (GCN20), member 2 TEA domain family member 4 TEAD4 2.5 <tr< td=""><td>12</td><td></td><td>TGFB-inducible early growth response</td><td>TIEG</td><td>3.3</td><td>4.3</td><td>3.8</td></tr<>	12		TGFB-inducible early growth response	TIEG	3.3	4.3	3.8
M25269 ELKI, member of ETS oncogene family ELKI 3.1 D78335 Uridine monophosphate kinase VM 3.2 M25804 Putative receptor protein PMI 2.4 A50803 Calcium/cabmodulin-dependent protein kinase kinase 2, β CAMKK2 2.1 L3801 Calcium/cabmodulin-dependent protein kinase kinase 3 β CAMKK2 2.1 L3801 L-3-hydroxyacyl-Coenzyme A dehydrogenase, short chain POLDI 2.5 M81735 Polymerase (DNA directed), δ I, catalytic subunit POLDI 2.7 M81735 Nucleolar protein I I catalytic subunit NOLI 2.7 M32110 Nucleolar protein I I catalytic subunit NOLI 2.7 M32110 Nucleolar protein I I catalytic subunit SRP-R 2.7 M73481 X-ray repair complementing defective repair in Chinese hamster cells 3 Chelk 2.5 D10704 Melanoma antigen, family F (GCN20), member 2 ABCF2 2.4 A1005016 ATP-binding cassette, sub-family F (GCN20), member 2 ABCF2 2.4 M5325 Pim-I o	8		Budding uninhibited by benzimidazoles I (yeast homolog)	BUBI	4.3	3.7	3.7
D78335 Uridine monophosphate kinase UMPK 3.2 X51804 Putative receptor protein X51804 PMI 2.4 X51804 Putative receptor protein Calcium/calmodulin-dependent protein 1.3 1.3 A8018330 Calcium/calmodulin-dependent protein GJycogen synthase kinase 3 β CAMKK2 2.1 A8018330 L-3-hydroxyacyl-Coenzyne A dehydrogenase, short chain HADHSC 3.2 M81735 Polymerase (DNA directed), δ 1, catalytic subunit POLDI 2.5 M81735 Polymerase (DNA directed), δ 1, catalytic subunit POLDI 2.7 M32110 Nucleolar protein I A dehydrogenase, short chain POLDI 2.7 AF03505 ELKL motif kinase AF0250 GRP-R 2.7 AF035586 X-ray repair complementing defective repair in Chinese hamster cells 3 XRCG3 2.5 AF035586 X-ray repair complementing defective repair in Chinese hamster cells 3 XRCG3 2.5 AF035586 X-ray repair complementing defective repair in Chinese hamster cells 3 XRCG3 2.5 A100301 ATP-binding cassette, su	6	_	ELK1, member of ETS oncogene family	ELKI	 	3.1	3.
X51804 Putative receptor protein AB018330 Calcium/calmodulin-dependent protein kinase kinase 2, β CAMKK2 2.1 Calcium/calmodulin-dependent protein kinase kinase 3, β L-3+ydroxyacyl-Coenzyne A dehydrogenase, short chain AF001903 L-3-hydroxyacyl-Coenzyne A dehydrogenase, short chain Polymerase (DNA directed), δ 1, catalytic subunit M32110 Nucleolar protein I X97630 ELKL motif kinase M73481 Gastrin-releasing peptide receptor AF035586 X-ray repair complementing defective repair in Chinese hamster cells 3 XRCC3 2.5 AF035586 X-ray repair complementing defective repair in Chinese hamster cells 3 Choline kinase M610000ma antigen, family A,3/6 Protein phosphatase 1G (formerly 2C), magnesium-dependent, gamma isoform PPM1G AB000509 TNF receptor-associated factor 5 A10932 TRAF5 2.2 AB000509 ATP-binding cassette, sub-family F (GCN20), member 2 TRAF5 2.5 AB000509 TNF receptor-associated factor 5 A106516 ATP-binding cassette, sub-family F (GCN20), member 2 TRAF5 2.2 AB00509 TNF receptor-associated factor 5 A106516 AG000000000000000000000000000000000000	20		Uridine monophosphate kinase	UMPK	3.5	3.1	3.1
AB018330 Calcium/calmodulin-dependent protein kinase 2, β CAMKK2 2.1 L33801 Calcium/calmodulin-dependent protein kinase AF001903 L-3-hydroxyacyl-Coenzyme A dehydrogenase, short chain AF0153 ASK38 3.2 AF001903 L-3-hydroxyacyl-Coenzyme A dehydrogenase, short chain POLD1 2.7 M32130 Potymerase (DNA directed), δ 1, catalytic subunit POLD1 2.7 M3210 Nucleolar protein I BMK1 2.4 M3210 ELKL motif kinase MOLD1 2.7 M73481 Gastrin-releasing peptide receptor GRP-R 2.7 AF035586 X-ray repair complementing defective repair in Chinese hamster cells 3 XRCC3 2.5 AF035586 X-ray repair complementing defective repair in Chinese hamster cells 3 XRCC3 2.5 AF035586 X-ray repair complementing defective repair in Chinese hamster cells 3 XRCC3 2.5 AF035586 X-ray repair complementing defective repair in Chinese hamster cells 3 XRCC3 2.5 AF035586 Y-ray repair complementing defective repair in Chinese hamster cells 3 XRCC3 2.3 ATP-binding cass	21		Putative receptor protein	PMI	2.4	3.7	m
L33801 Glycogen synthase kinase 3 β AF001903 L-3-hydroxyacyl-Coenzyme A dehydrogenase, short chain HADHSC 3.2 M81735 Polymerase (DNA directed), δ 1, catalytic subunit POLD1 2.5 M82110 Nucleolar protein 1 X97630 Gastrin-releasing peptide receptor Gastrin-releasing peptide receptor AF035586 X-ray repair complementing defective repair in Chinese hamster cells 3 XRCC3 2.7 AF035586 X-ray repair complementing defective repair in Chinese hamster cells 3 XRCC3 2.5 AF035586 X-ray repair complementing defective repair in Chinese hamster cells 3 XRCC3 2.5 AF035586 X-ray repair complementing defective repair in Chinese hamster cells 3 XRCC3 2.5 AF035586 X-ray repair complementing defective repair in Chinese hamster cells 3 XRCC3 2.5 AF035586 X-ray repair complementing defective repair in Chinese hamster cells 3 XRCC3 2.5 AF00509 Protein phosphatase 1G (formerly 2C), magnesium-dependent, gamma isoform PPM1G 2.3 AB00509 TINF receptor-associated factor 5 AB00509 TIRAF5 2.2 AF050506 ATP-binding cassette, sub-family F (GCN20), member 2 TEAD4 2.5 AF050506 ATP-binding cassette, sub-family F (GCN20), member 2 TEAD4 2.5 AF050506 ATP-binding cassette, sub-family F (GCN20), member 2 ABCF2 2.4 AF050509 Pin-1 oncogene CCND1 CCND1 2.3 AF050509 Proteasome subunit, β 1ype, 2 Araf-1 murine leukemia viral oncogene homolog 1 RAF1 2.3	22		Calcium/calmodulin-dependent protein kinase kinase 2, \beta	CAMKK2	2.1	3.7	2.9
AF001903 L-3-hydroxyacyl-Coenzyme A dehydrogenase, short chain HADHSC 3.2 M81735 Polymerase (DNA directed), δ 1, catalytic subunit POLDI 2.5 M32110 Nucleolar protein 1 Xy37630 ELKL motif kinese Portein 1 AF03586 X-ray repair complementing defective repair in Chinese hamster cells 3 Choline kinase Choline kinase Choline kinase Choline kinase Protein phosphatase 1G (formerly 2C), magnesium-dependent, gamma isoform PPM1G 2.1 AB000509 ATP-binding cassette, sub-family F (GCN20), member 2 TEA domain family member 4 M5382 TEA domain family member 4 M54915 Pim-1 oncogene Choline protein phosphatase 1G (cornell phosphatas	23	_	Glycogen synthase kinase 3 β	GSK3B	3.2	5.6	2.9
M81735 Potymerase (DNA directed), δ 1, catalytic subunit POLD1 2.5 M32110 Nucleolar protein 1 2.7 X97630 ELKL motif kinase ELKL motif kinase 2.4 M73481 Gastrin-releasing peptide receptor GRP-R 2.7 A73481 X-ray repair complementing defective repair in Chinese hamster cells 3 XRCG3 2.7 Choline kinase Choline kinase MAGE-A3/6 2.1 D10704 Melanoma antigen, family A.3/6 CHK 3 Y13936 Protein phosphatase 1G (formerly 2C), magnesium-dependent, gamma isoform PPM1G 2.3 A1005016 ATP-binding cassette, sub-family F (GCN20), member 2 TEAF5 2.2 A105016 ATP-binding cassette, sub-family F (GCN20), member 2 TEAD4 2.5 A10532 Pim-1 oncogene CCND1 2.1 X59798 Cyclin D1 Carebellar degeneration-related protein PSMB2 2.2 D26599 Proteasome subunit, β 1ype, 2 CDR2 2.3 X03484 V-raf-1 murine leukemia viral oncogene homolog 1 2.3	24	•	L-3-hydroxyacyl-Coenzyme A dehydrogenase, short chain	HADHSC	3.2	5.6	2.9
M32110 Nucleolar protein 1 NOL1 2.7 X97630 ELKL motif kinase EMK1 2.4 M73481 Gastrin-releasing peptide receptor GRP-R 2.7 AF035586 X-ray repair complementing defective repair in Chinese hamster cells 3 XRCC3 2.5 Choline kinase Choline kinase MAGE-A3/6 2.1 D10039 Melanoma antigen, family A.3/6 MAGE-A3/6 2.1 Y13936 Protein phosphatase 1G (formerly 2C), magnesium-dependent, gamma isoform PPM1G 2.3 A1005016 ATP-binding cassette, sub-family F (GCN20), member 2 TRAF5 2.2 A105016 ATP-binding cassette, sub-family F (GCN20), member 2 TEAD4 2.5 M54915 Pim-1 oncogene CCND1 2.1 X59798 Cyclin D1 Crebellar degeneration-related protein CDR2 2.2 D26599 Proteasome subunit, β 1ype, 2 RAF1 2.3 X03484 V-raf-1 murine leukemia viral oncogene homolog 1 RAF1 2.3	25	_	Polymerase (DNA directed), § 1, catalytic subunit	POLDI	2.5	3.3	2.9
X97630 ELKL motif kinase EMK1 2.4 M73481 Gastrin-releasing peptide receptor GRP-R 2.7 AF035586 X-ray repair complementing defective repair in Chinese hamster cells 3 XRCC3 2.5 D10704 Choline kinase CHK 3 Choline kinase Gramming A,3/6 MAGE-A3/6 2.1 Y13936 Protein phosphatase 1G (formerly 2C), magnesium-dependent, gamma isoform PPM1G 2.3 AB000509 TNF receptor-associated factor 5 ARCC3 2.2 A1005016 ATP-binding cassette, sub-family F (GCN20), member 2 TRAF5 2.2 A10405016 ATP-binding cassette, sub-family F (GCN20), member 2 TRAF5 2.5 A39415 Pim-1 oncogene CCND1 2.5 A59416 Cyclin D1 CCND1 2.1 M63226 Cerebellar degeneration-related protein PSMB2 2.2 D26599 Proteasome subunit, β type, 2 RAF1 2.3 X03484 V-raf-1 murine leukemia viral oncogene homolog 1 RAF1 2.3	56		Nucleolar protein 1	NOLI	2.7	m ·	2.8
M73481 Gastrin-releasing peptide receptor A73481 GRF-R 2.7 AF035586 X-ray repair complementing defective repair in Chinese hamster cells 3 XRCC3 2.5 D10704 Choline kinase Choline kinase AAGE-A3/6 2.1 V13936 Protein phosphatase 1G (formerly 2C), magnesium-dependent, gamma isoform PPM1G 2.3 AB000509 TNF receptor-associated factor 5 ABCC2 2.4 A1005016 ATP-binding cassette, sub-family F (GCN20), member 2 TRAF5 2.2 A1005016 ATP-binding cassette, sub-family F (GCN20), member 2 TRAF5 2.2 A1005016 ATP-binding cassette, sub-family F (GCN20), member 2 TRAF5 2.2 A39050 ATP-binding cassette, sub-family F (GCN20), member 2 TEAD4 2.5 M54915 Pim-1 oncogene CCND1 2.1 Cyclin D1 Cretebellar degeneration-related protein PSMB2 2.2 D26599 Proteasome subunit, β type, 2 RAF1 2.3 X03484 V-raf-1 murine leukemia viral oncogene homolog 1 2.3	77	•	ELKL motif kinase	EMKI	2.4	333	6, 6 80 1
AF035S6 X-ray repair complementing defective repair in Chinese hamster cells 3 XRCC3 2.5 CHOline kinase Choline kinase MAGE-A3/6 2.1 V10339 Melanoma antigen, family A,3/6 Protein phosphastase 1G (formerly 2C), magnesium-dependent, gamma isoform PPM1G 2.3 TNF receptor-associated factor 5 A1005016 ATP-binding cassette, sub-family F (GCN20), member 2 ABCF2 2.4 ABCF2 1.6 AFP-binding cassette, sub-family F (GCN20), member 2 ABCF2 2.4 AFP-binding cassette, sub-family F (GCN20), member 2 ABCF2 2.2 AFP-binding cassette, sub-family F (GCN20), member 2 CCND1 2.5 AFF1 2.2 AFF1 2.3 A	78	_	Gastrin-releasing peptide receptor	GRP-R	2.7	7.7	2.7
D10704 Choline kinase Chik 3 U10339 Melanoma antigen, family A,3/6 MAGE-A3/6 2.1 A100339 Melanoma antigen, family A,3/6 PPM IG 2.1 A100509 TPY receptor-associated factor 5 1 1 A1005016 ATP-binding cassette, sub-family F (GCN20), member 2 ABCF2 2.4 U6382 TEA domain family member 4 1 1 M54915 Pim-1 oncogene CCND1 2.2 M6382 Cerebellar degeneration-related protein CCND1 2.2 M6383 Proteasome subunit, β type, 2 ESMB2 2.2 Notas599 Proteasome subunit, β type, 2 FSMB2 2.2 X03484 V-raf-1 murine leukemia viral oncogene homolog 1 RAF1 2.3	23	_	X-ray repair complementing defective repair in Chinese hamster cells 3	XRCC3	5.5	ć	2.7
Melanoma antigen, family A,3/6 Y13936 Protein phosphatase 1G (formerty 2C), magnesium-dependent, gamma isoform PPM1G 2.3 AB000509 TNF receptor-associated factor 5 A1005016 ATP-binding cassette, sub-family F (GCN20), member 2 TEAP4 2.2 A1005016 ATP-binding member 4 TEAP4 2.2 M54912 Pim-1 oncogene CCND1 2.1 M63256 Cerebellar degeneration-related protein D26599 Proteasome subunit, β type, 2 Noraf-1 murine leukemia vital oncogene homolog 1 RAF1 2.3 X03484 V-raf-1 murine leukemia vital oncogene	30		Choline kinase	CHK		7.3	7.0 7.0
Y13936 Protein phosphatase 1G (formerly 2C), magnesium-dependent, gamma isotorm PPM1G 2.3 AB000509 TNF receptor-associated factor 5 12 A1005016 ATP-binding cassette, sub-family F (GCN20), member 2 ABGF2 2.4 A10382 AFA domain family member 4 ABGF2 2.4 M54915 Pim-1 oncogene CCND1 2.1 X59798 Cerebellar degeneration-related protein CDR2 2.2 D26599 Proteasome subunit, β type, 2 PSMB2 2.2 X03484 V-raf-1 murine leukemia viral oncogene homolog 1 RAF1 2.3	31	_	Melanoma antigen, family A,3/6			~ (5.5
AB000509 TNF receptor-associated factor 5 AB000509 TNF receptor-associated factor 5 ABCF2 2.4 A1005016 ATP-binding cassette, sub-family F (GCN20), member 2 ABCF2 2.4 M54915 Pim-1 oncogene PIM1 2.2 M54915 Cyclin Di CCND1 2.1 M63256 Cerebellar degeneration-related protein CDR2 2.2 D26599 Proteasome subunit, β type, 2 PSMB2 2.2 X03484 V-raf-1 murine leukemia viral oncogene homolog 1 RAF1 2.3	32	•	Protein phosphatase 1G (formerly 2C), magnesium-dependent, gamma isolorm		2.3	7 0	2.5
A1005016 ATP-binding cassette, sub-family F (GCN20), member 2 ABCF2 2.4 U6382 TEA domain family member 4 2.5 M54915 Pim-1 oncogene PIM1 2.2 M54919 Cyclin DI CCND1 2.1 M63218 Cyclin DI CCND1 2.1 M63226 Cerebellur degeneration-related protein CDR2 2.2 D26599 Proteasome subunit, β type, 2 FSMB2 2.2 X03484 V-raf-1 murine leukemia viral oncogene homolog l RAF1 2.3	33	•	TNF receptor-associated factor 5	IKAFS	7.7	7.7	4.7
U6382 TEA domain family member 4 1.2 M54915 Pim-1 oncogene 2.2 M54916 Pim-1 oncogene 2.1 Cyclin DI 2.1 M63256 Cerebellar degeneration-related protein CDR2 2.2 D26599 Proteassome subunit, β type, 2 FSMB2 2.2 X03484 V-raf-1 murine leukemia viral oncogene homolog l RAF1 2.3	8	-	ATP-binding cassette, sub-family F (GCN20), member 2	ABCF2	4.6	2.5	2.4
M54915Pim-1 oncogene2.2X59798Cyclin D12.1M63256Cerebellar degeneration-related proteinCDR22.2D26599Proteasome subunit, β type, 2PSMB22.2X03484V-raf-1 murine leukemia viral oncogene homolog lRAF12.3	35	_	TEA domain family member 4	LEAD4	7.7	7.7	2.3
X59798 Cyclin D1 M63256 Cerebellar degeneration-related protein D26599 Proteasome subunit, β type, 2 X03484 V-raf-1 murine leukemia viral oncogene homolog 1 RAF1 2.3	36		Pim-1 oncogene	Pimi	7.7	7.7	7.7
M63256 Cerebellar degeneration-related protein CDK2 2.2 D26599 Proteasome subunit, β type, 2 X03484 V-raf-1 murine leukemia viral oncogene homolog 1 RAF1 2.3	37	•	Cyclin D1	CCND	7.7	7.7	7 .
D26599 Proteasome subunit, \(\beta \) type, 2 X X03484 V-raf-1 murine leukemia viral oncogene homolog 1 RAF1	38		Cerebellar degeneration-related protein	CDK2	7.7	7.7	7.7
X03484 V-rai-1 murine leukemia viral oncogene nomolog i	33		Proteasome subunit, \(\beta \) type, 2	FSIVID2 DAE:	7.7	7 .	7 .
	40		V-rai-1 murine leukemia viral oncogene nomolog i	KALI	C.4	٠	7:1

Genes that are downregulated more than 2.0-fold in response to the enhanced expression of RB2/p130 by microarray analysis are listed. Genes were identified as unique as mentioned in the GenBank¹¹¹ and are sorted in descending order. Ratio 1 indicates the fold of repression for each gene as determined by microarray analysis of H23-Ad-CMV vs H23-Ad-CMV-RB2/p130. Ratio 2 indicates the fold of repression for each gene as determined by microarray analysis of H23 vs H23-Ad-CMV-RB2/p130

Table 2	Classification	of RB2/p130-repre	essed genes by category
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Table 2	Classification of RB2/p130-repressed	genes by category
Category		Genes
ATPase/G	TPase/ATP binding/GTP binding	ABCF2 KNSL2
Calcium/po	otassium/sodium/iron binding protein	CAMKK2
Cell cycle/c	cyclins	BUBI BUBIB CCNBI CCNB2 CCNDI CCNF B-MYB NOLI PCNA PLK PPMIG
Cell surface	e/antigen	ABCF2 CDR2 GPRK6 GRP-R KNSL2 MAGE-A 3/6 PCNA PMI
Chromoson	ne/chromatin/histone	DNMT1 PLK XRCC3
Cytokines a	ind growth factors	GRP-R PCSK7 TIEG TRAF5
Cytoskeleto	n/microtubules/microfilaments/motility	CAMKK2 EMK1 KNSL2
Differentiat	ion/development	BUBI GSK3B B-MYB NOLI PIMI PLK RAFI TEAD4 TIEG
Diseases		B-MYB CCND1 CDR2 ELK1 MAGE-A 3/6 NOL1 PCSK7 PIM1 RAF1 STK15
DNA bindir	ng/damage/recombination	DNMTI POLDI XRCC3
G protein/re	gulators of G protein signaling	GPRK6 GRP-R PMI
Hydrolase/h	ydrolysis/hydrolyses	ABCF2 PCSK7 PPM1G

Table 2 Continued	
Category	Genes
Kinases	BUBI BUBIB CAMKK2 CHK ELKI EMKI GPRK6 GSK3B MKK3 NIK PLK RAFI STK15 UMPK
Lipoproteins/lipids	СНК
Membrane trafficking	DNMTI KPNA2
Mitochondrial proteins	ABCF2 HADHSC
Nuclear receptors/receptors	BUBI DNMTI ELKI GPRK6 GRP-R NOLI PCNA PMI POLDI PPMIG TIEG TRAF5
Oncogenes	B-MYB ELKI PIMI RAFI
Phosphatase/proteases/peptidase	PCSK7 PPM1G PSMB2
Signal transduction	CAMKK2 GPRK6 GRP-R MKK3 NIK PMI TRAF5
Synthetase/synthase	GSK3B PFAS
Transcription/transcription factor	B-MYB CDR2 ELK1 HCFCI TEAD4 TIEG
Transporters Transferases	ABCF2 DNMTI PFAS

The analysed genes are classified on the basis of established biological or pathological functions of the encoded proteins. Genes that are listed in one category are indicated in bold

WHAT IS CLAIMED IS:

1. A method of determining whether to use a RB2/p130 gene expression system or a protein encoded by the system to modulate a gene or gene expression pattern in lung cancer cells of a human test subject, the method comprising:

providing molecular signatures modulated by RB2/p130 for lung cancer cells, wherein the molecular signatures comprise expression products of at least one of the genes selected from the group consisting of: PCNA, MKK3, B-MYB, CCNF, BUB1B,PLK, NIK, KNSL2, PCSK7, CCNB2, GPRK6, HCFC1, PFAS, DNMT1, KPNA2, STK15, TIEG, BUB1 ELK1, UMPK, PMI, CAMKK2, GSK3B, HADHSC, POLD1, NOL1, EMK1, GRP-R, XRCC3, CHK, MAGEA3/6, PPM1G, TRAF5, ABCF2, TEAD4, PIM1, CCND1, CDR2, PSMB2 and RAF1;

determining gene or genes expressed in the lung cancer cells of the human test subject; and

using the RB2/p130 gene expression system or the protein to modulate the gene or the gene expression pattern in the lung cancer cells of the human test subject if it is determined that the gene or genes expressed in the lung cancer cells of the human test subject are the same as the at least one of the genes.

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- 2. The method of claim 1 wherein the genes selected are B-MYB, PCSK7, STK15, ELK1, NOL1, MAGEA3/6, PIM1, CCND1, CDR2, and RAF1.
- 3. The method of claim 1, wherein the human test subject is posttreatment for a non-small cell lung cancer.
 - 4. The method of claim 3, wherein the treatment is selected from the group consisting of surgical operation, chemotherapy, radiation therapy and RB2/p130 gene therapy or combinations thereof.

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PCT/US2004/032286

1/5

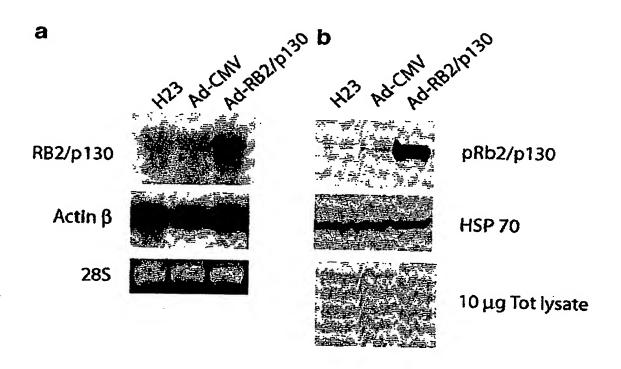


FIGURE 1

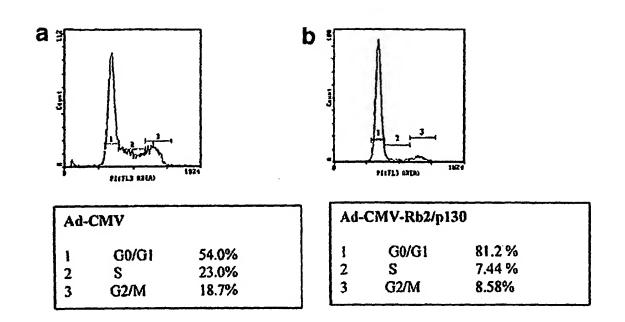
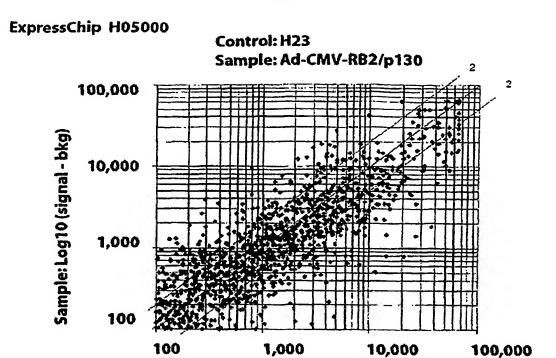
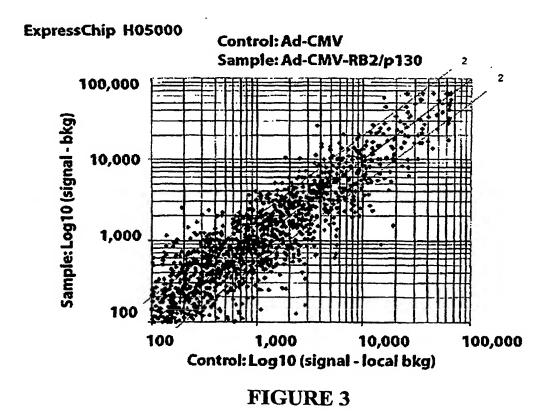


FIGURE 2

3/5



Control: Log10 (signal - local bkg)



4/5

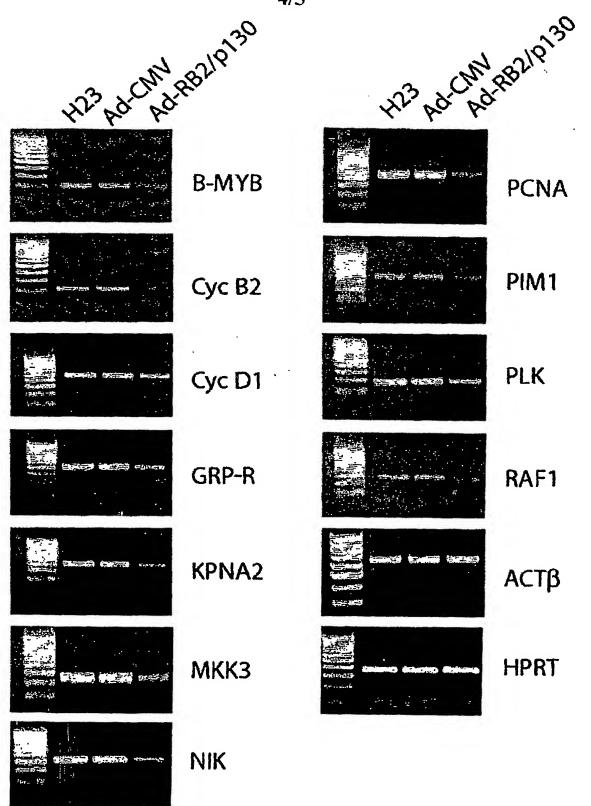


FIGURE 4

PCT/US2004/032286

5/5

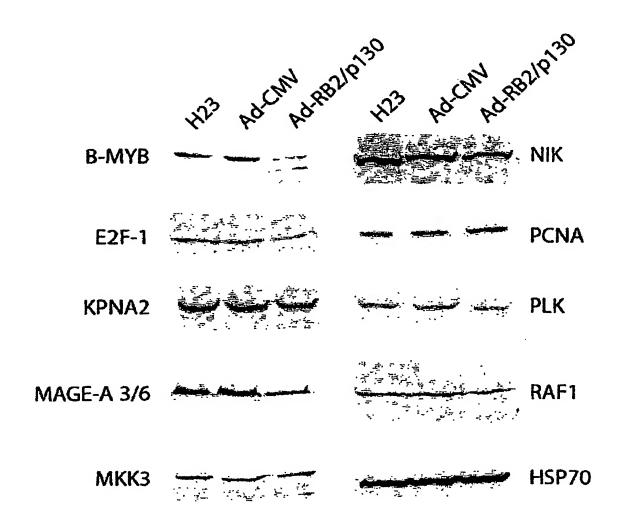


FIGURE 5